# The complement system and obesity-associated metabolic disorders

# Valorisation addendum

The ultimate aim of scientific research is to transfer the research findings into practice, via which they can not only contribute to academic but also to society and economy. This process is called valorisation. In this chapter, the social and economic value of our findings and how they can be translated into practical use are discussed.

## 1 Social and economic relevance

Obesity is a rising epidemic worldwide. According to a survey of 195 countries in 2017, the prevalence of obesity has continuously increased and has doubled in most of the countries in the past 3 decades (1). The higher prevalence of obesity can have a negative impact on society and the economy (2). First, obese individuals have a lower quality of life due to impaired psychological and physical health (3). For instance, individuals with obesity may experience emotional and psychological problems (e.g. lower self-esteem, anxiety, and depression) that result from perceived lower social acceptance. They may also experience physical problems, such as back pain and shortness of breath. Such psychological and physical impairments in obese individuals can lead to a lower employment rate, which may further reduce their quality of life. Second, obese individuals are at a higher risk for obesity-related diseases, such as hypertension, T2DM, CVD, and cancer, which are related to higher morbidity and mortality. In 2015, global deaths among adults due to high BMI (BMI equal to or greater than 22.5 kg/m$^2$, which is the midpoint of the optimal range of 20-25 kg/m$^2$) were estimated to be 4 million, and about 60% of them occurred in obese individuals (1). In addition, the above-mentioned obesity-related issues can all contribute to increased economic burden on the individuals, their family, and the society due to higher costs of health care, as well as productivity losses (4). In 2014, the estimated worldwide economic impact of obesity is 2.0 trillion dollars, which equals 2.8 percent of global gross domestic product (5). Therefore, efforts on controlling the (global) prevalence and incidence, as well as the (health) consequences, of obesity is in urgent need. For this purpose, steps could be taken to explore the related intervention programs and to provide better predictions of obese individuals with higher risk to develop comorbid conditions. In addition, we must

obtain better knowledge of the aetiology of obesity and its health consequences prior to these attempts.

In this thesis, we showed that the complement system, especially the alternative complement pathway, was associated with the prevalence and the development of adiposity. We also found that higher plasma levels of (some) alternative pathway components were associated with several common metabolic disorders related to obesity, including adverse lipoprotein profile, higher prevalence and incidence of metabolic syndrome, worse insulin resistance and higher prevalence and incidence of T2DM. Although our present findings cannot be directly applied to real practice and policy development, it proposed the possibility for plasma complement components to serve as candidate biomarkers in risk prediction of these obesity-associated metabolic disorders, and as a novel target for disease treatment.

## 2 Target group

Our main findings on the possible aetiological role of the complement system in obesity and related metabolic disorders can benefit other academics by adding novel knowledge on the pathophysiological mechanisms on obesity and its complications. For instance, the current results can provide basis for relevant future intervention programs by inducing the possibility of plasma complement markers as intervention targets or as treatment response markers. It can also promote the pharmaceutical companies to develop novel therapeutic drugs targeting complement reduction for the treatment of chronic metabolic disease. In addition, our findings on the potential predictive and therapeutic value of these blood complement markers can help healthcare professionals with decision making in medicine and health care, after its clinical application.

## 3 Innovation and implementation

Our studies investigated in humans the associations of complement, not only the most discussed central complement factor C3 but also its regulators and activation products, with

a series of obesity-related metabolic disorders. Our current findings confirmed and expanded the previously reported role of C3 in cardiometabolic diseases in our study population. For the associations of other complement components with these disorders, our data fill the knowledge gap in humans, since such information was, previously, mainly derived from animal studies. We observed in **chapter 4** and **chapter 5**, positive associations of C3, but not other complement regulators and activation products, with the incidence of metabolic syndrome and T2DM. Our results thus indicate potential biological effects for individual complement components, which may independent of complement activation, the commonly accepted underlying route in these pathophysiological processes. We also found in **chapter 3** that the associations of most alternative pathway components with lipoproteins were independent of C3. In **chapter 6**, we showed the intricate associations of plasma markers of dicarbonyl stress with complement activation. It can facilitate future research on the underlying mechanisms of the association between them, which may contribute to a better understanding of cardiovascular complications in diabetes.

In this thesis, we observe elevated plasma levels of alternative pathway components in metabolic disorders in middle-aged to elderly Caucasian individuals with moderately increased risk of cardiometabolic disease. In our prospective studies in **chapter 2**, **3**, **4**, we also show that higher plasma level of C3, and to a lesser extent C4 and factor H, are associated with the development of obesity and related metabolic disorders, such as metabolic syndrome and T2DM. Our findings thus suggest a potential role for plasma complement as predictive biomarkers in clinical practice. They can also contribute to personalized health care by their potential function as a supplementary marker for classical risk factors in selecting high-risk individuals. Other potential future applications of our findings include the preventive and therapeutic value of plasma complement markers in the treatment of chronic metabolic disorders. For instance, they could help to guide the therapeutic interventions of these diseases. The effect of lifestyle interventions (6-10) and some commonly prescribed medications (11-14) on limiting systemic levels of some complement components have been reported previously. This potential beneficial effect on complement and its application in diseases prevention and treatment should be further investigated in large-scale randomized clinical trials. In addition, plasma levels of these

complement markers can be used to evaluate the effect of medical treatment on these metabolic diseases. Lastly, our findings raise the possibility of a novel therapeutic strategy for these metabolic diseases that targeting the reduction of blood complement levels. As discussed in **chapter 7**, future studies are needed to develop sensitive, accurate, effective, and lower cost complement modifying drugs, which take into account the multiple functions of the complement system in humans. Possible directions for drug development may include anti-complement antibodies, small molecular inhibitors for complement, as well as blockers for the relevant effector pathways. Nevertheless, further technical and clinical validation and standardization of these complement markers are necessary prior to their clinical application. Plasma level of C3, the most abundant complement components, is widely used in the clinic and is generally regarded as a marker of inflammation or immune response that are most likely linked to diseases like acute infection or autoimmune disease. Similar to what is seen in other human studies investigating the cardiometabolic risk of C3 in the general population or in specific populations (e.g. individuals with obesity or T2DM), the distribution of C3 in our study population is mostly within the normal reference range (15). Although a moderately higher C3 concentration has been consistently shown to be present in and/or to predict chronic metabolic diseases, a reliable cut-off reference for abnormal C3 concentration under these disease conditions is still lacking. Future exploration of this aspect, which should also take into account the characteristics of the target population (e.g. age, sex, ethnicity), is needed for its clinical use.

Taken together, with the investigations in this thesis we show a potential role of complement in obesity and related metabolic disorders. Our results may open new paths for the prediction, prevention, and/or treatment of these diseases. Efforts on validation, standardization, as well as intervention programs will be critical to warrant future clinical practice.

## References


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